

WHAT IS CLAIMED IS:

1. A method of treating or inhibiting a disease state in a mammal which can be alleviated by concurrent inhibition of neutral endopeptidase and the metalloprotease IGS5, wherein said metalloprotease IGS5 is a polypeptide comprising an amino acid sequence which has at least 70% identity to an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4 and SEQ ID NO:6, said method comprising administering to said mammal an effective amount of a compound, or pharmaceutically acceptable salt thereof, having inhibitory activity

- a) on neutral endopeptidase and
- b) on said metalloprotease IGS5.

2. The method of claim 1, wherein said compound is present as a solvate or as a biolabile ester.

3. The method of claim 1, wherein said disease state is characterized by elevated big-ET-1 levels and wherein said disease state can be alleviated or inhibited by administering an effective amount of a compound having combined inhibitory activity on neutral endopeptidase and on IGS5.

4. The method of claim 1, wherein said disease state is characterized by upregulation of ET-1 and wherein said disease state can be alleviated or inhibited by administering an effective amount of a compound having combined inhibitory activity on neutral endopeptidase and on IGS5.

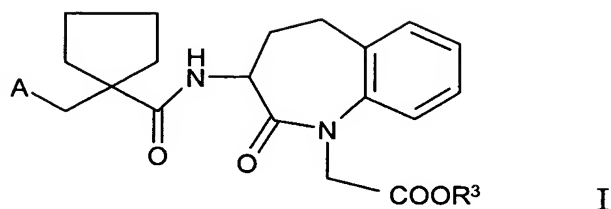
5. The method of claim 1, wherein said disease state includes at least one condition selected from the group consisting of hypertension, heart failure, angina pectoris, arrhythmias, myocardial infarction, cardiac hypertrophy, cerebral ischemia, peripheral vascular disease, subarachnoidal hemorrhage, chronic obstructive pulmonary disease, asthma, renal disease, atherosclerosis, and pain in colorectal cancer or prostate cancer.

6. The method of claim 5, wherein said disease state is renal hypertension or pulmonary hypertension.

7. The method of claim 1, wherein said metalloprotease is a polypeptide comprising an amino acid sequence which has at least 95% identity to an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4 and SEQ ID NO:6.

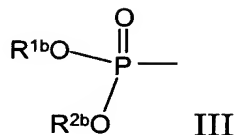
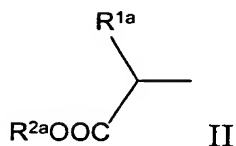
8. The method of claim 1, wherein said metalloprotease is a polypeptide comprising an amino acid sequence which is identical to an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4 and SEQ ID NO:6.

9. A method of treating or inhibiting a disease state in a mammal which can be alleviated by inhibiting neutral endopeptidase and the metalloprotease IGS5, wherein said metalloprotease IGS5 is a polypeptide comprising an amino acid sequence which has at least 70% identity to an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4 and SEQ ID NO:6, said method comprising administering to said mammal an effective amount of a compound corresponding to formula I,



wherein

A corresponds to formula II or III



wherein in formula II

R¹ᵃ is a phenyl-lower-alkyl group or a naphthyl-lower-alkyl group,

R²ᵃ is hydrogen or a group forming a biolabile ester; and

wherein in formula III

R¹ᵇ is hydrogen or a group forming a biolabile phosphonic acid ester,

R²ᵇ is hydrogen or a group forming a biolabile phosphonic acid ester;

and

R³ is hydrogen or a group forming a biolabile ester;

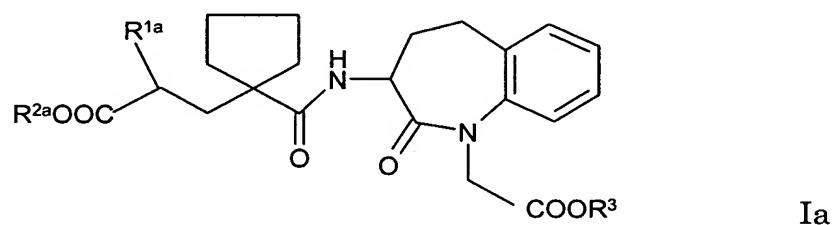
or a pharmaceutically acceptable salt thereof.

10. The method of claim 9, wherein R¹ᵃ is a phenyl-lower-alkyl group which is substituted in the phenyl ring by lower alkyl, lower alkoxy or halogen.

11. The method of claim 9, wherein R^3 is a group forming a biolabile carboxylic acid ester.

12. The method of claim 9, wherein said compound is in the form of a solvate or of a biolabile ester.

13. The method of claim 9, said method comprising administering to said mammal an effective amount of a compound corresponding to formula Ia,

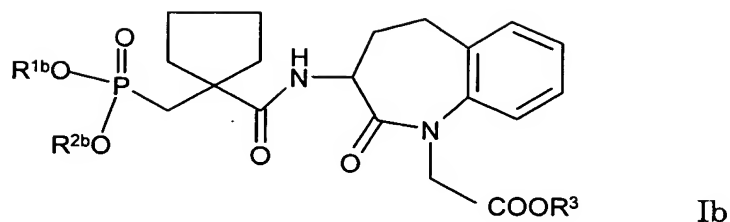


or a pharmaceutically acceptable salt thereof.

14. The method of claim 13, wherein R^{1a} is a phenyl-lower-alkyl group which is substituted in the phenyl ring by lower alkyl, lower alkoxy or halogen.

15. The method of claim 13, wherein said compound is in the form of a solvate.

16. The method of claim 9, said method comprising administering to said mammal an effective amount of a compound corresponding to formula Ib,



or a pharmaceutically acceptable salt thereof.

17. The method of claim 16, wherein R^3 is a group forming a biolabile carboxylic acid ester.

18. The method of claim 16, wherein said compound is in the form of a solvate.

19. The method of claim 9, wherein said disease state is characterized by elevated big-ET-1 levels.

20. The method of claim 9, wherein said disease state is characterized by upregulation of ET-1.

21. The method of claim 9, wherein said disease state includes at least one condition selected from the group consisting of hypertension, heart failure, angina pectoris, arrhythmias, myocardial infarction, cardiac hypertrophy, cerebral ischemia, peripheral vascular disease, subarachnoidal hemorrhage, chronic obstructive pulmonary disease, asthma, renal disease, atherosclerosis, and pain in colorectal cancer or prostate cancer.

22. The method of claim 21, wherein said disease state is renal hypertension or pulmonary hypertension.

23. The method of claim 19, wherein said disease state includes at least one condition selected from the group consisting of hypertension, heart failure, angina pectoris, arrhythmias, myocardial infarction, cardiac hypertrophy, cerebral ischemia, peripheral vascular disease, subarachnoidal hemorrhage, chronic obstructive pulmonary disease, asthma, renal disease, atherosclerosis, and pain in colorectal cancer or prostate cancer.

24. The method of claim 20, wherein said disease state includes at least one condition selected from the group consisting of hypertension, heart failure, angina pectoris, arrhythmias, myocardial infarction, cardiac hypertrophy, cerebral ischemia, peripheral vascular disease, subarachnoidal hemorrhage, chronic obstructive pulmonary disease, asthma, renal disease, atherosclerosis, and pain in colorectal cancer or prostate cancer.

25. The method of claim 9, wherein said metalloprotease is a polypeptide comprising an amino acid sequence which has at least a 95% identity to an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4 and SEQ ID NO:6.

26. The method of claim 9, wherein said metalloprotease is a polypeptide comprising an amino acid sequence which is identical to an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4 and SEQ ID NO:6.

27. The method of claim 1, further comprising administering to said mammal an additional metalloprotease inhibitor.

28. The method of claim 27, wherein said additional metalloprotease inhibitor is selected from the group consisting of angiotensin converting enzyme inhibitors, selective endothelin converting enzyme inhibitors, selective neutral endopeptidase inhibitors, dual neutral endopeptidase/endothelin converting enzyme inhibitors, and mixed inhibitors of these metalloproteases.

29. The method of claim 27, wherein said compound having inhibitory activity and said additional metalloprotease inhibitor are co-effective.

30. The method of claim 27, wherein said compound having inhibitory activity and said additional metalloprotease inhibitor are synergistically effective.

31. The method of claim 9, further comprising administering to said mammal an additional metalloprotease inhibitor.

32. The method of claim 31, wherein said additional metalloprotease inhibitor is selected from the group consisting of angiotensin converting enzyme inhibitors, selective endothelin converting enzyme inhibitors, selective neutral endopeptidase inhibitors, dual neutral endopeptidase/endothelin converting enzyme inhibitors, and mixed inhibitors of these metalloproteases.

33. The method of claim 31, wherein the compound corresponding to formula I and the additional metalloprotease inhibitor are co-effective.

34. The method of claim 31, wherein the compound corresponding to formula I and the additional metalloprotease inhibitor are synergistically effective.

35. The method of claim 13, further comprising administering to said mammal an additional metalloprotease inhibitor.

36. The method of claim 35, wherein said additional metalloprotease inhibitor is selected from the group consisting of angiotensin converting enzyme inhibitors, selective endothelin converting enzyme inhibitors, selective neutral endopeptidase inhibitors, dual neutral endopeptidase/endothelin converting enzyme inhibitors, and mixed inhibitors of these metalloproteases.

37. The method of claim 35, wherein the compound corresponding to formula Ia and the additional metalloprotease inhibitor are co-effective.

38. The method of claim 35, wherein the compound corresponding to formula Ia and the additional metalloprotease inhibitor are synergistically effective.

39. The method of claim 16, further comprising administering to said mammal an additional metalloprotease inhibitor.

40. The method of claim 39, wherein said additional compound is a metalloprotease inhibitor selected from the group consisting of angiotensin converting enzyme inhibitors, selective endothelin converting enzyme inhibitors, selective neutral endopeptidase inhibitors, dual neutral endopeptidase/endothelin converting enzyme inhibitors, and mixed inhibitors of these metalloproteases.

41. The method of claim 39, wherein the compound corresponding to formula Ib and the additional compound are co-effective.

42. The method of claim 39, wherein the compound corresponding to formula Ib and the additional metalloprotease inhibitor are synergistically effective.

43. A pharmaceutical composition for inhibiting at least one metalloprotease, comprising:

a first compound having inhibitory activity for neutral endopeptidase and inhibitory activity for the metalloprotease IGS5, wherein said metalloprotease IGS5 is a polypeptide comprising an amino acid sequence which has at least 70% identity to an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4 and SEQ ID NO:6, or a pharmaceutically acceptable salt thereof;

at least one additional metalloprotease inhibitor, and

a pharmaceutically acceptable carrier.

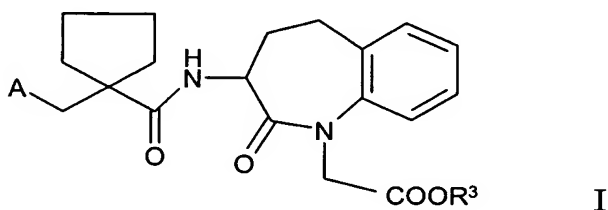
44. The pharmaceutical composition of claim 43, wherein said additional metalloprotease inhibitor is selected from the group consisting of angiotensin converting enzyme inhibitors, selective endothelin converting enzyme inhibitors, selective neutral endopeptidase inhibitors, dual neutral endopeptidase/endothelin converting enzyme inhibitors, and mixed inhibitors of these metalloproteases.

45. The pharmaceutical composition of claim 43, wherein said first compound and said at least one additional metalloprotease inhibitor are co-effective.

46. The pharmaceutical composition of claim 43, wherein said first compound and said at least one additional metalloprotease inhibitor are synergistically effective.

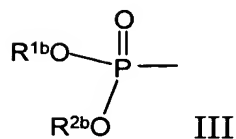
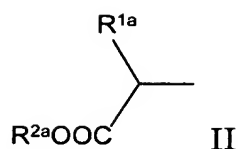
47. The pharmaceutical composition of claim 43, wherein said first compound is in the form of a solvate or of a biolabile ester.

48. The pharmaceutical composition of claim 43, wherein said first compound corresponds to the structure of formula I,



wherein

A corresponds to formula II or III



wherein in formula II

R^{1a} is a phenyl-lower-alkyl group or a naphthyl-lower-alkyl group,

R^{2a} is hydrogen or a group forming a biolabile ester; and

wherein in formula III

R^{1b} is hydrogen or a group forming a biolabile phosphonic acid ester,

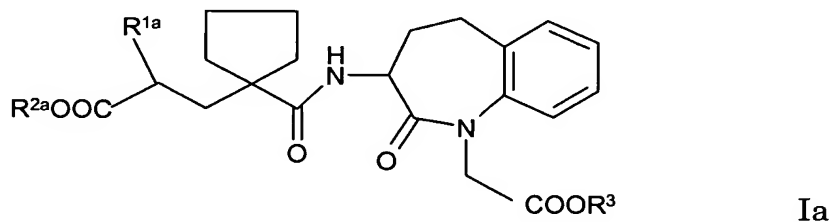
R^{2b} is hydrogen or a group forming a biolabile phosphonic acid ester;

and

R³ is hydrogen or a group forming a biolabile ester;

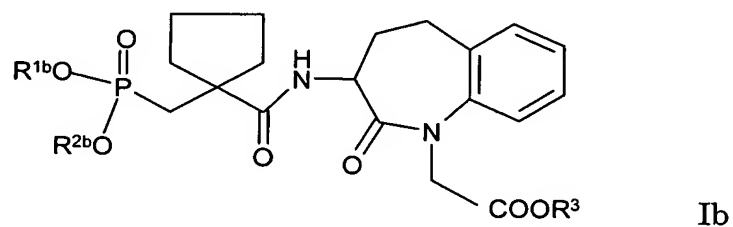
or a pharmaceutically acceptable salt thereof.

49. The pharmaceutical composition of claim 48, wherein said first compound corresponds to the structure of formula Ia,



or a pharmaceutically acceptable salt thereof.

50. The pharmaceutical composition of claim 48, wherein said first compound corresponds to the structure of formula Ib,



or a pharmaceutically acceptable salt thereof.